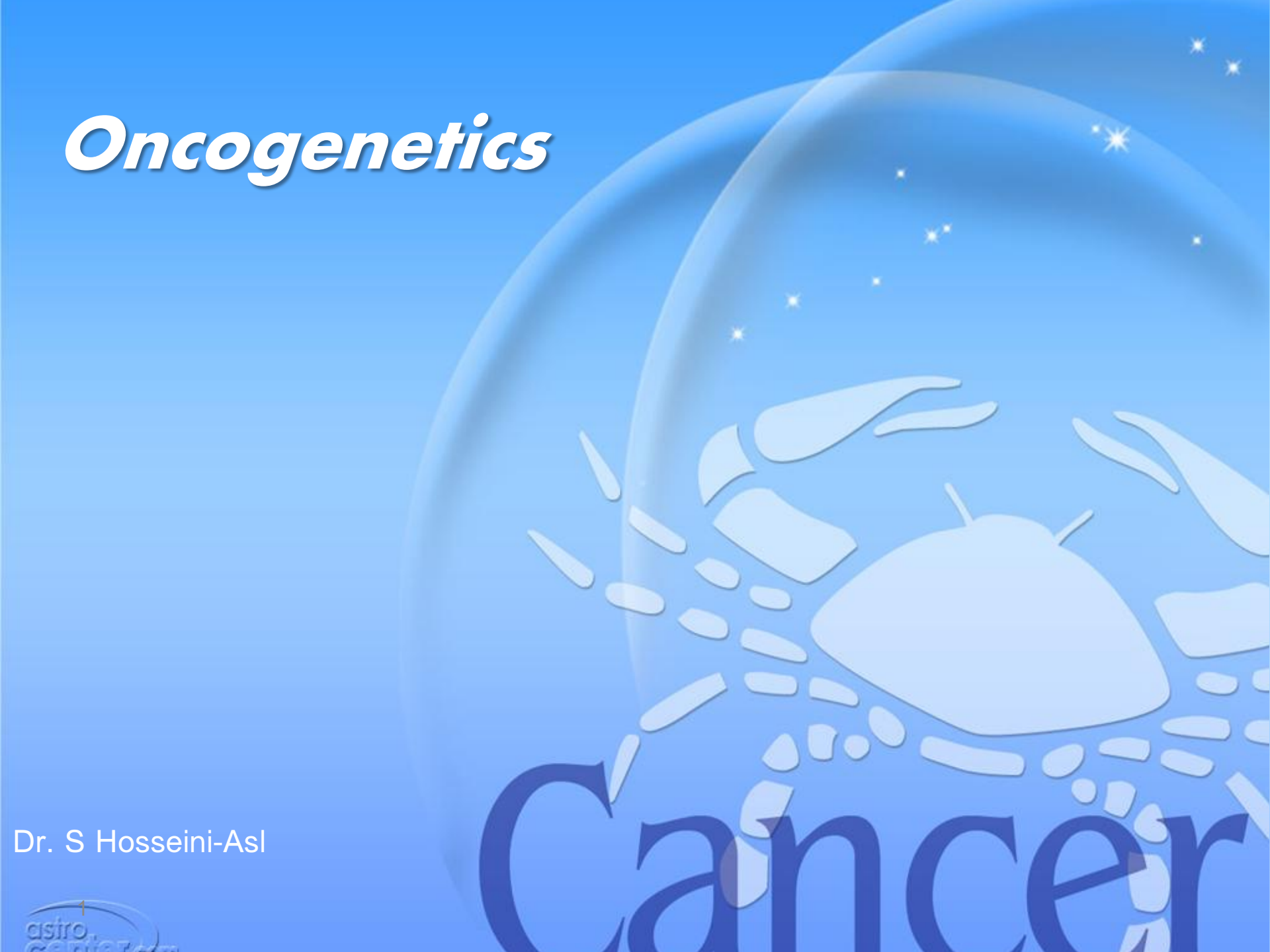
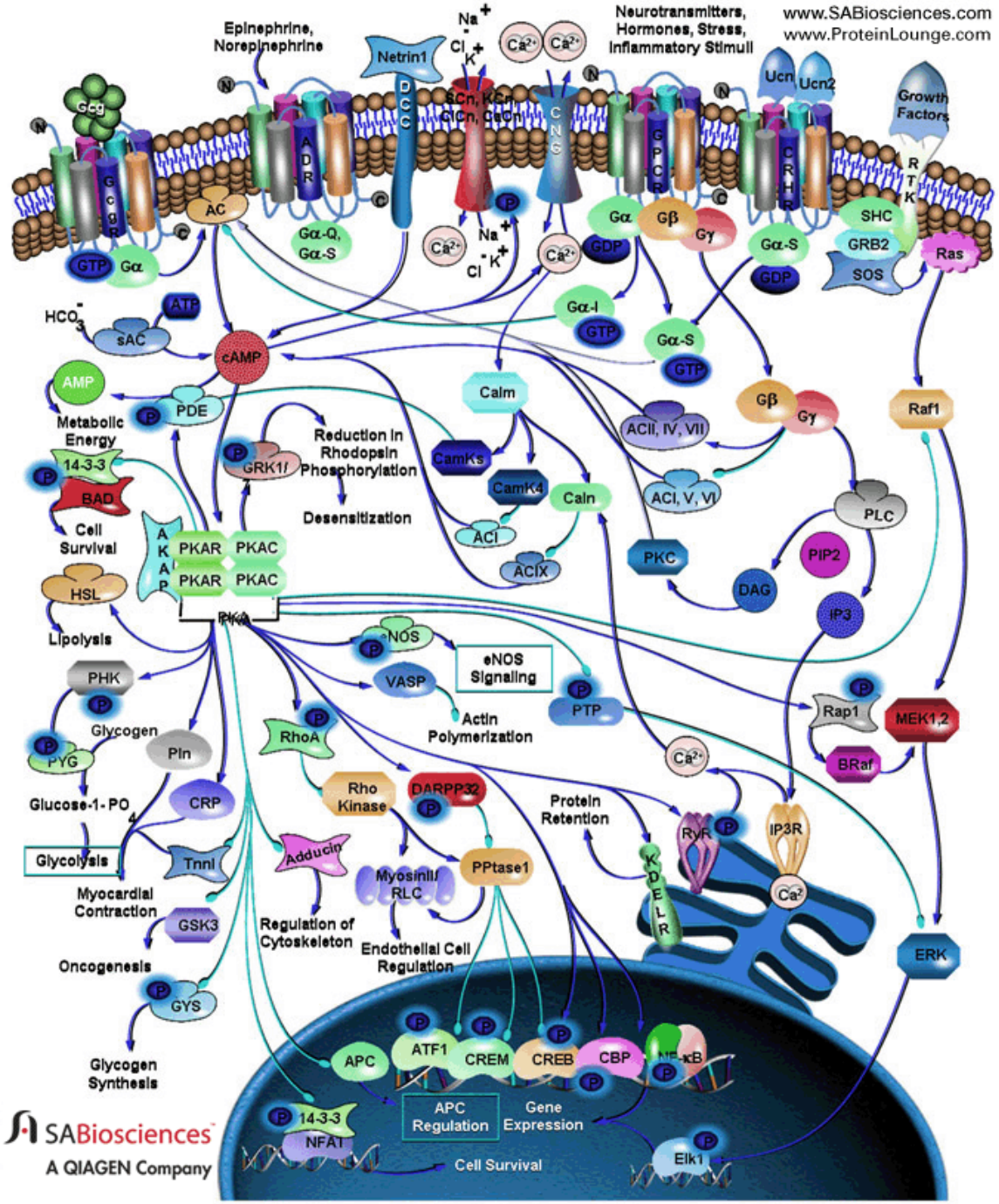
Oncogenetics



Dr. S Hosseini-Asl


Epinephrine, Norepinephrine
Netrin1
Neurotransmitters, Hormones, Stress, Inflammatory Stimuli
www.SABiosciences.com
www.ProteinLounge.com
Ucn
Ucn2
Growth Factors
Gcg
AC
Gα-Q, Gα-S
GTP
Gα
ATP
HCO3-
sAC
cAMP
AMP
Metabolic Energy
PDE
14-3-3
BAD
Cell Survival
HSL
Lipolysis
AKAP
PKAR
PKAC
PKA
GRK1/
Reduction in Rhodopsin Phosphorylation
Desensitization
Calm
CamKs
CamK4
Caln
ACI
ACIX
ACII, IV, VII
ACI, V, VI
Gβ
Gγ
PLC
PKC
PIP2
DAG
IP3
Raf1
Gα-I
Gα-S
GDP
SHC
GRB2
SOS
Ras
RTK
eNOS
VASP
eNOS Signaling
PTP
Actin Polymerization
Rap1
MEK1,2
BRaf
PHK
Glycogen
PYG
Pln
Glucose-1-PO
CRP
Glycolysis
TnnI
Myocardial Contraction
GSK3
Oncogenesis
GYS
Glycogen Synthesis
RhoA
Rho Kinase
DARPP32
Adducin
Myosin II/ RLC
PPtase1
Regulation of Cytoskeleton
Endothelial Cell Regulation
Protein Retention
RyR
IP3R
KDELR
ERK
APC
ATF1
CREM
CREB
CBP
NF-κB
APC Regulation
Gene Expression
14-3-3
NFAT
Cell Survival
Elk1
SABiosciences
A QIAGEN Company

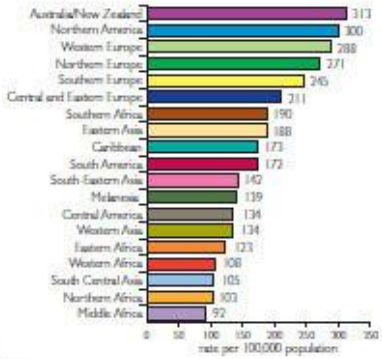
CANCER RESEARCH UK

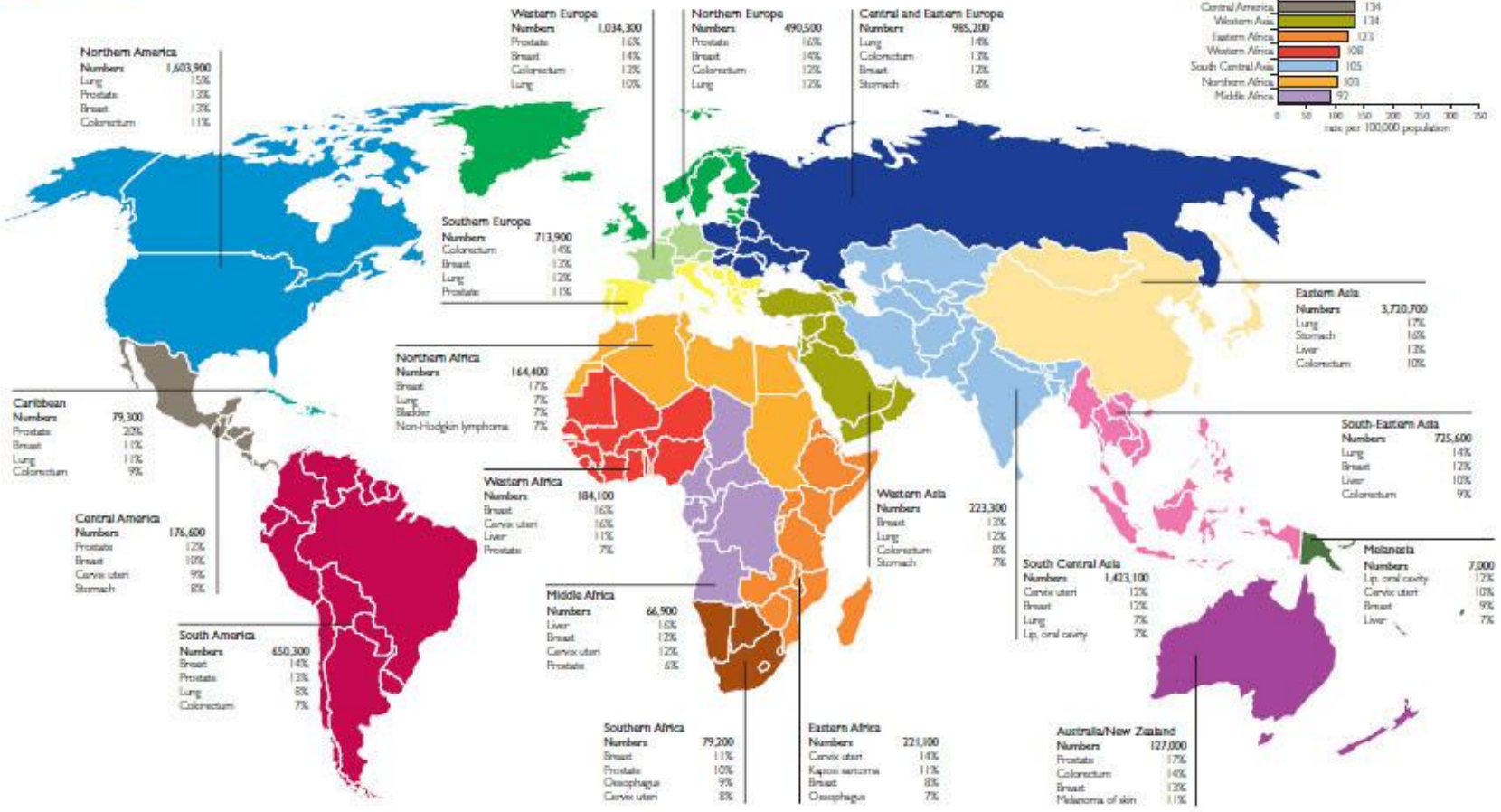
International Agency for Research on Cancer

World Health Organization

Cancer Incidence Worldwide

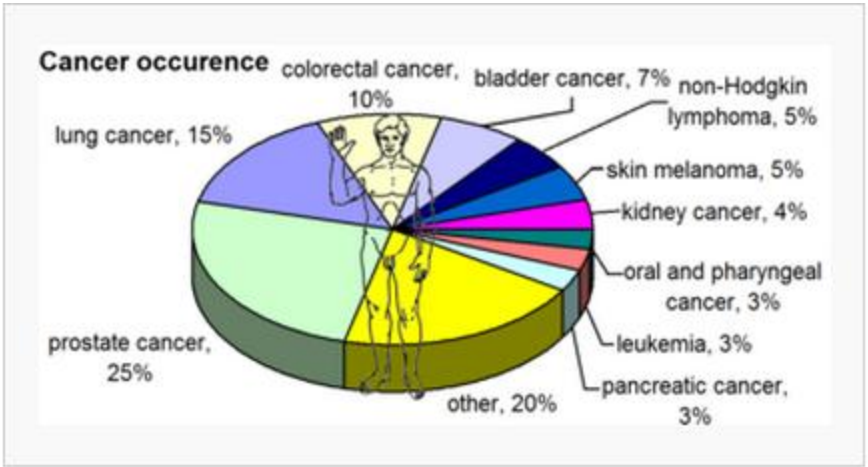
Breakdown of the estimated 12.7 million new cases, age standardised incidence rates and the most commonly diagnosed cancers by the different regions of the world, 2008.



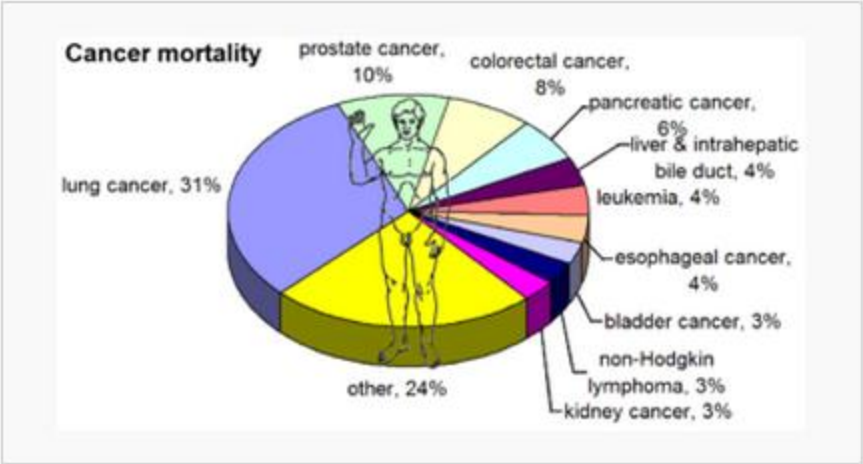


Source: GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide. IARC, 2010 (http://globocan.iarc.fr)

http://info.cancerresearchuk.org/cancerstats/

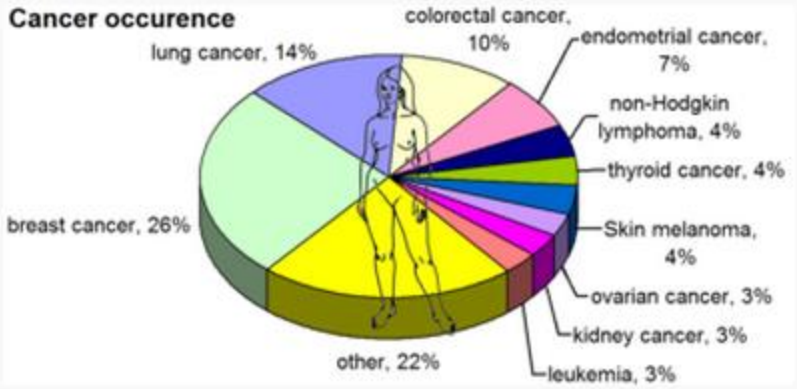


Most common cancers in US males, by occurrence[14]

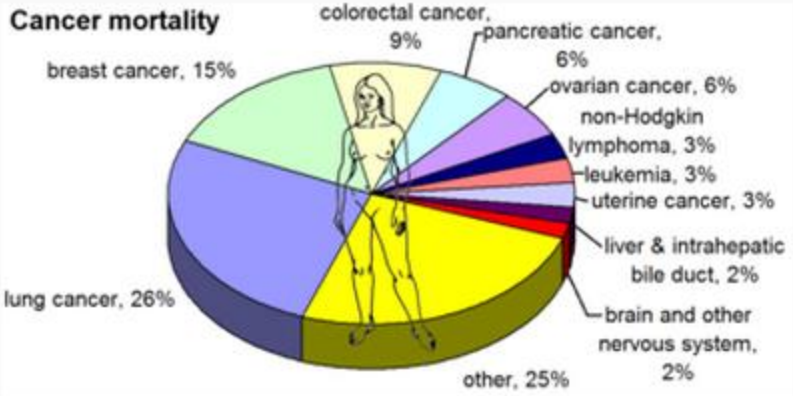


in US males, by mortality[14]

Male	
most common (by occurrence)[14]	**most common (by mortality)**[14]
prostate cancer (25%)	lung cancer (31%)
lung cancer (15%)	prostate cancer (10%)
colorectal cancer (10%)	colorectal cancer (8%)
bladder cancer (7%)	pancreatic cancer (6%)
non-Hodgkin lymphoma (5%)	liver & intrahepatic bile duct (4%)
skin melanoma (5%)	leukemia (4%)
kidney cancer (4%)	esophageal cancer (4%)
oral and pharyngeal cancer (3%)	bladder cancer (3%)
leukemia (3%)	non-Hodgkin lymphoma (3%)
pancreatic cancer (3%)	kidney cancer (3%)
other (20%)	other (24%)

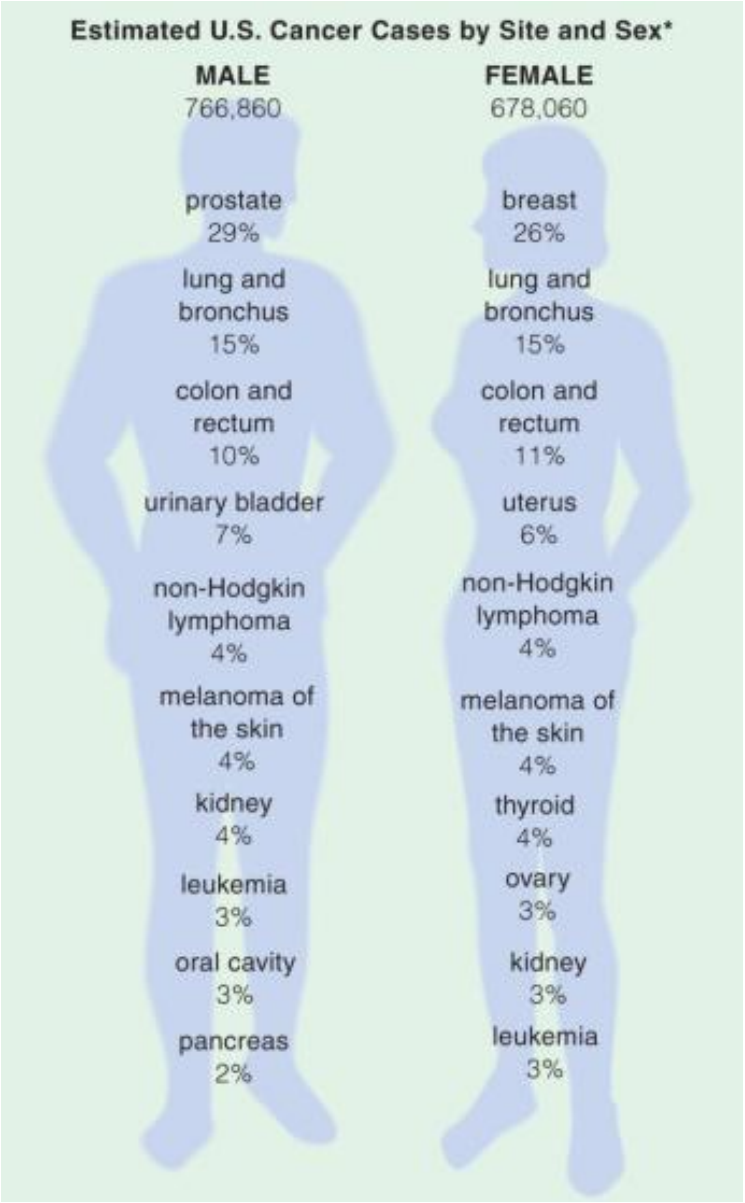


in US females, by occurrence[14]



in US females, by mortality[14]

Female	
most common (by occurrence)[14]	**most common (by mortality)**[14]
breast cancer (26%)	lung cancer (26%)
lung cancer (14%)	breast cancer (15%)
colorectal cancer (10%)	colorectal cancer (9%)
endometrial cancer (7%)	pancreatic cancer (6%)
non-Hodgkin lymphoma (4%)	ovarian cancer (6%)
thyroid cancer (4%)	non-Hodgkin lymphoma (3%)
Skin melanoma (4%)	leukemia (3%)
ovarian cancer (3%)	uterine cancer (3%)
kidney cancer (3%)	liver & intrahepatic bile duct (2%)
leukemia (3%)	brain and other nervous system (2%)
other (22%)	other (25%)


Estimated U.S. Cancer Cases by Site and Sex*
MALE
766,860
prostate
29%
lung and bronchus
15%
colon and rectum
10%
urinary bladder
7%
non-Hodgkin lymphoma
4%
melanoma of the skin
4%
kidney
4%
leukemia
3%
oral cavity
3%
pancreas
2%
FEMALE
678,060
breast
26%
lung and bronchus
15%
colon and rectum
11%
uterus
6%
non-Hodgkin lymphoma
4%
melanoma of the skin
4%
thyroid
4%
ovary
3%
kidney
3%
leukemia
3%

Early and accurate diagnosis of cancer is important to maximize the chances that a cancer can be cured

Test or Procedure	Cancer	Sex	Age	Frequency
Breast self-examination	Breast	Female	20+	Monthly
Mammogram	Breast	Female	40–49	Every 1–2 years
			50+	Yearly
Testicle self-examination	Testicle	Male	18+	Monthly
Sigmoidoscopy	Colon	Male, Female	50+	Every 3–5 years
Fecal occult blood test	Colon	Male, Female	50+	Yearly
Digital rectal examination	Prostate, colorectal	Male, Female	40+	Colorectal: Yearly Prostate:Yearly up to age 75
Pap test	Uterus, cervix	Female	18+ and all sexually active women	Every other year until age 35; yearly thereafter
Pelvic examination	Uterus, ovaries, cervix	Female	18–39 40+	Every 1–3 years w/Pap, yearly
General checkup		Male, Female	20–39	Every 3 years
			40+	Yearly

The genetic basis of cancer

- The human body is composed of a multitude of different cell types and tissues.
- Cancers can arise from all of these. What we broadly call cancer is actually a diverse spectrum of human diseases, a few of which constitute a mere nuisance while most others are deadly.

- The most common cancers in adults are *carcinomas,* derived from epithelial cells that line body cavities and glands.
- *Sarcomas arise from* mesenchymal tissues. Melanomas, retinoblastomas, neuroblastomas and glioblastomas are derived from dividing cells in the ocular retina, neurons and neural glia respectively.
- Lymphomas and leukemias, sometimes referred to as the liquid tumors, arise in the tissues that give rise to lymphoid and blood cells.

- The cancer gene theory has provided a framework for understanding how both hereditary and environmental factors contribute to cancers.

Neoplasm vs. Tumor

- A *neoplasm (literally 'a new growth') is any abnormal new growth of cells,* whereas a *tumor is a neoplasm that is associated with a disease state.*
- *Tumors are* diseases in which a population of genetically related cells has acquired the ability to proliferate abnormally.

Cancer

- The term ‘cancer’ simply defines those tumors which have acquired the ability to invade surrounding tissues composed of normal cells. The distinction between a *benign and a malignant tumor is solely based on* this invasive capacity. If an invading malignant tumor reaches a blood or lymphatic vessel, a cancer can *metastasize and grow in distant tissues.*

Tumorogenesis

- The growth of a tumor from the progeny of this one cell is a process known as *tumorigenesis.*
- *As tumors grow from* small, benign lesions to malignant and then metastatic cancers, the cells that compose these tumors change genetically and thereby acquire new properties.

Cancer gene

- A cancer gene can be defined as a variant of a gene that increases cancer risk, or promotes the development of cancer.
- there are two types of cells in the human body.
- *Germ cells are the cells of the reproductive system that produce sperm in males and* oocytes in females. *Somatic cells, derived from the Greek work for body, soma, are* all other cells exclusive of the germ cells. Cancer genes that arise in the germ cells are said to be in the *germline. Individuals who inherit germline cancer genes will* carry a germline cancer gene in every cell, somatic cells and germ cells alike. Such individuals are aptly known as *carriers. In contrast, cancer genes that arise in* somatic cells are not passed on to subsequent generations.

- The mutations that define cancer genes can be acquired in three ways:
- (1) inheritance via the germline,
- (2) spontaneously via somatic mutation,
- (3) via viral infection.

Many different alterations in genomic DNA can convert normal genes to cancer genes.

- 1. Point mutation
- 2. Chromosomal mutations
- 3. Epigenetic

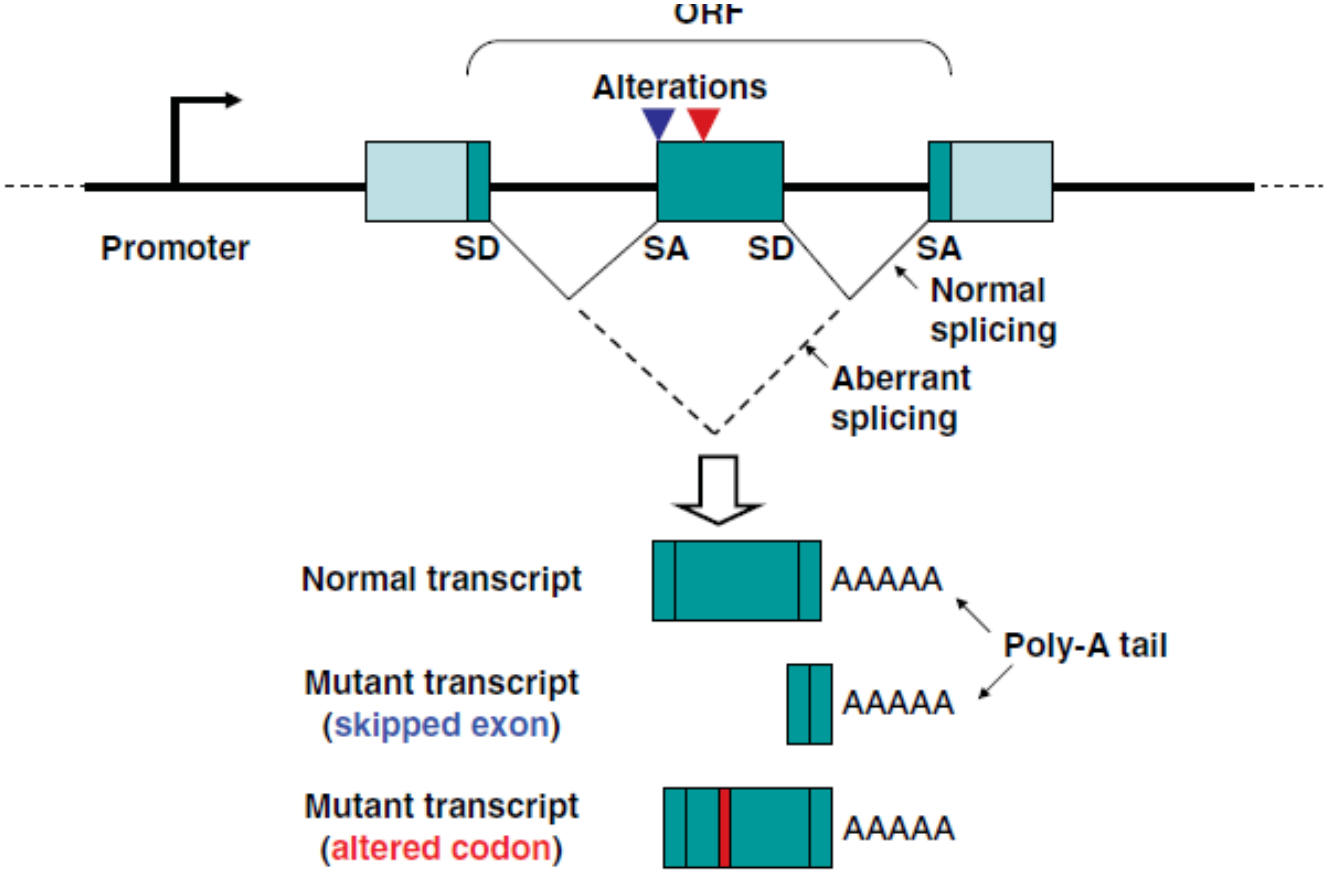


Fig. 1.4 Mutations can alter gene transcripts. The majority of the mutations that create cancer genes alter codons (example shown in red). About 10% of mutations interfere with RNA processing by disrupting the splice donor (SD) or splice acceptor (SA) consensus sequences. Such mutations (example shown in blue) cause aberrant RNA splicing that can result in exon skipping

- Mutations in promoter elements, transcriptional initiation sites, intiation codons, polyadenylation sites and termination codons have also been shown to alter gene function.
- All of these together account for less than 2% of all mutations known to cause human disease, including cancer.

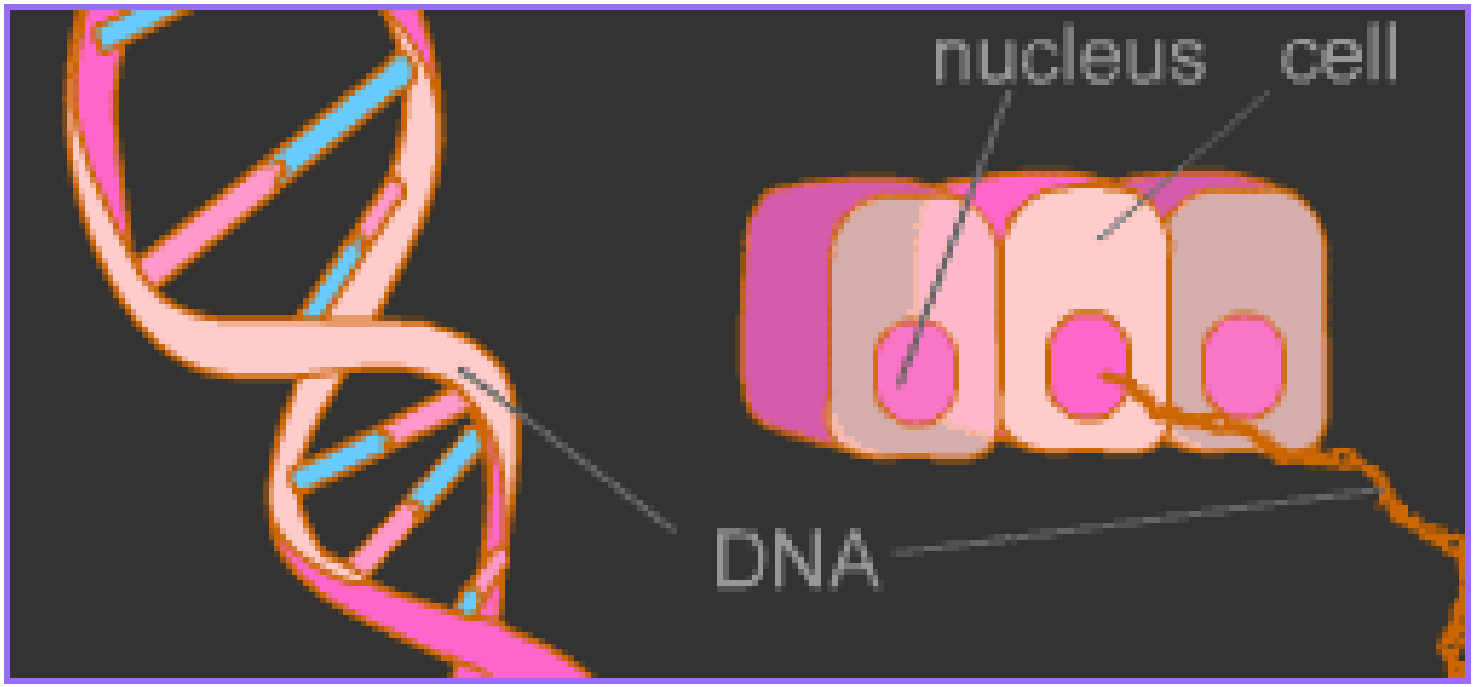
Polymorphisms and cancer susceptibility

- The most common form of genetic variation between humans is the *single nucleotide polymorphism, or SNP (pronounced 'snip').*
- *When the genomic DNA sequences of* two individual, homologous chromosomes are compared, SNPs occur, on average, every 1,000–2,000 bp. It is estimated that there are about 10–12 million different SNPs in the human population. Roughly 4% of SNPs occur in exons; most exons are within 5,000 bp of the nearest SNP.

MTHFR C677T

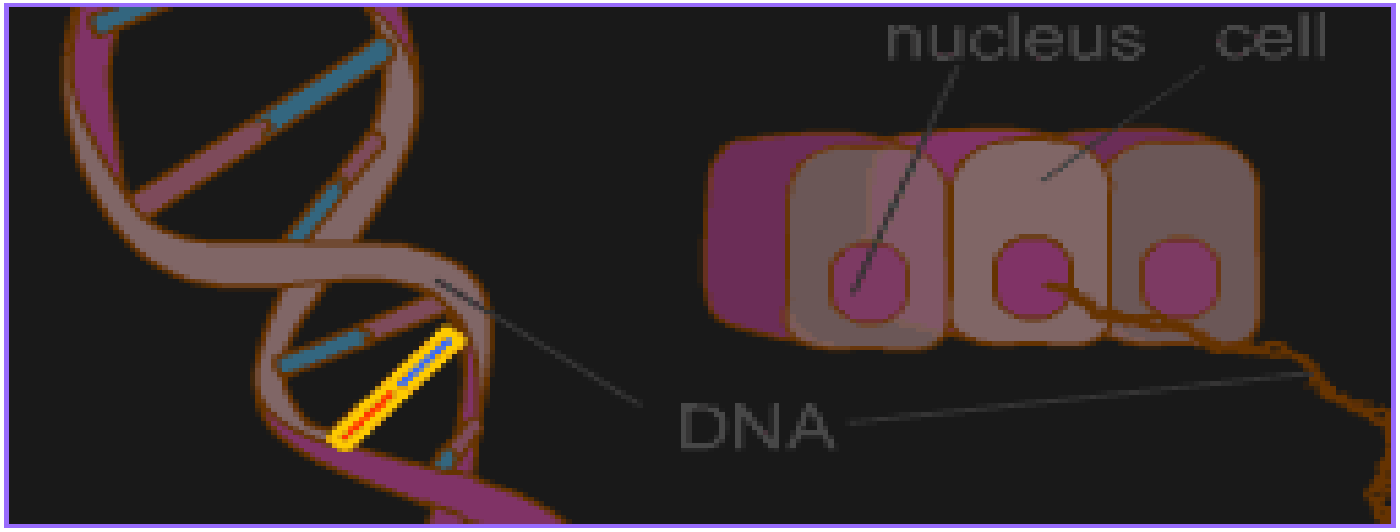
- The MTHFR nucleotide at position 677 in the gene has two possibilities: C or T. C at position 677 (leading to an alanine at amino acid 222) is the normal allele. The 677T allele (leading to a valine substitution at amino acid 222) encodes a thermolabile enzyme with reduced activity.
- Individual with two copies of 677C (677CC) have the "normal" or "wildtype" genotype. 677TT individuals (homozygous) are said to have mild MTHFR deficiency. 677CT individuals (heterozygotes) are almost the same as normal individuals because the normal MTHFR can make up for the thermolabile MTHFR. About ten percent of the North American population are T-homozygous for this polymorphism. There is ethnic variability in the frequency of the T allele – frequency in Mediterranean/Hispanics is greater than the frequency in Caucasians which, in turn, is greater than in Africans/African-Americans.
- The degree of enzyme thermolability (assessed as residual activity after heat inactivation) is much greater in 677TT individuals (18-22%) compared with 677CT (56%) and 677CC (66-67%). Individuals of 677TT are predisposed to mild hyperhomocysteinemia (high blood homocysteine levels), because they have less active MTHFR available to produce 5-methyltetrahydrofolate (which is used to decrease homocysteine). Low dietary intake of the vitamin folic acid can also cause mild hyperhomocysteinemia.
- Low folate intake affects individuals with the 677TT genotype to a greater extent than those with the 677CC/CT genotypes. 677TT (but not 677CC/CT) individuals with lower plasma folate levels are at risk for elevated plasma homocysteine levels. In studies of human recombinant MTHFR, the protein encoded by 677T loses its FAD cofactor three times faster than the wild-type protein. 5-Methyl-THF slows the rate of FAD release in both the wild-type and mutant enzymes, although it is to a much greater extent in the mutant enzyme. 677TT individuals are at a decreased risk for certain leukemias and colon cancer.

DNA of a normal cell



- This piece of DNA is an exact copy of the DNA from which it came. When the parent cell divided to create two cells, the cell's DNA also divided, creating two identical copies of the original DNA.

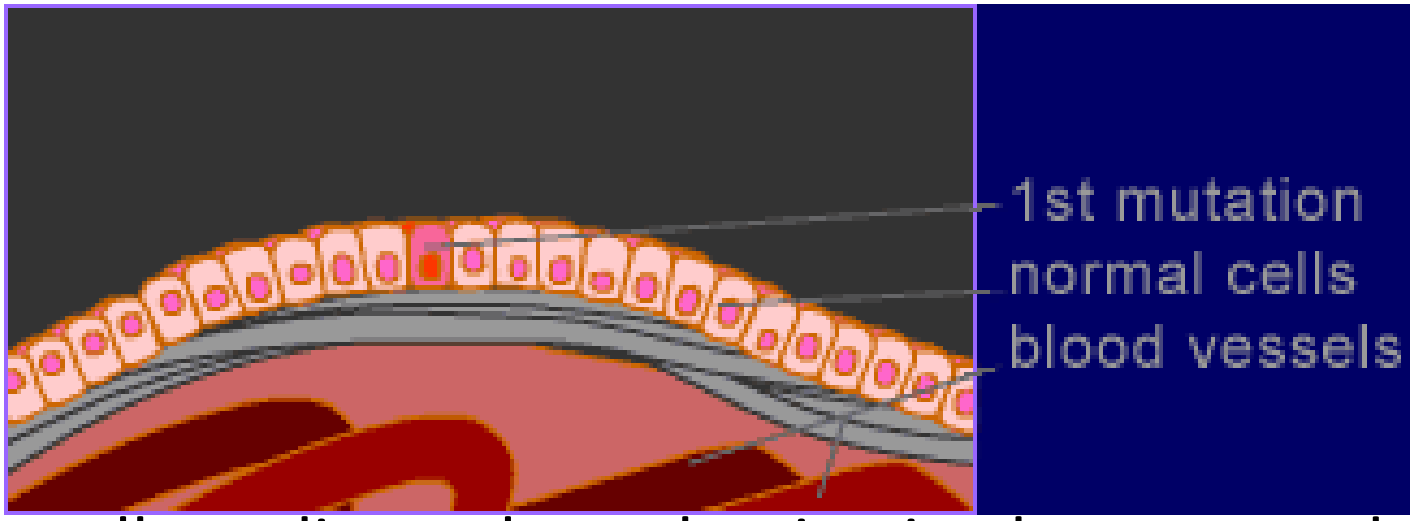
Mutation of DNA



- Here is the same section of DNA but from another cell. If you can imagine that DNA is a twisted ladder, then each rung of the ladder is a pair of joined molecules, or a base pair. With this section of DNA, one of the base pairs is different from the original.

  This DNA has suffered a mutation, either through mis-copying (when its parent cell divided), or through the damaging effects of exposure to radiation or a chemical carcinogen.

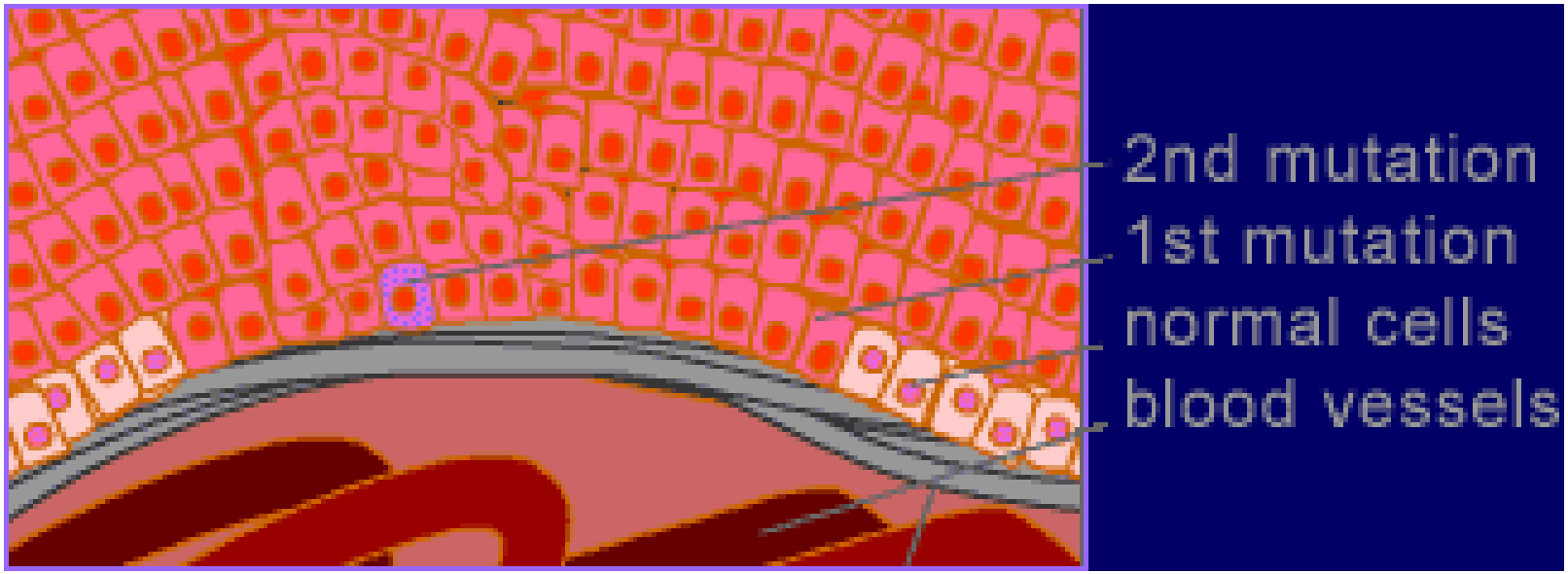
Genetically altered cell



- Body cells replicate through mitosis, they respond to their surrounding cells and replicate only to replace other cells. Sometimes a genetic mutation will cause a cell and its descendants to reproduce even though replacement cells are not needed.

  The DNA of the cell highlighted above has a mutation that causes the cell to replicate even though this tissue doesn't need replacement cells at this time or at this place.

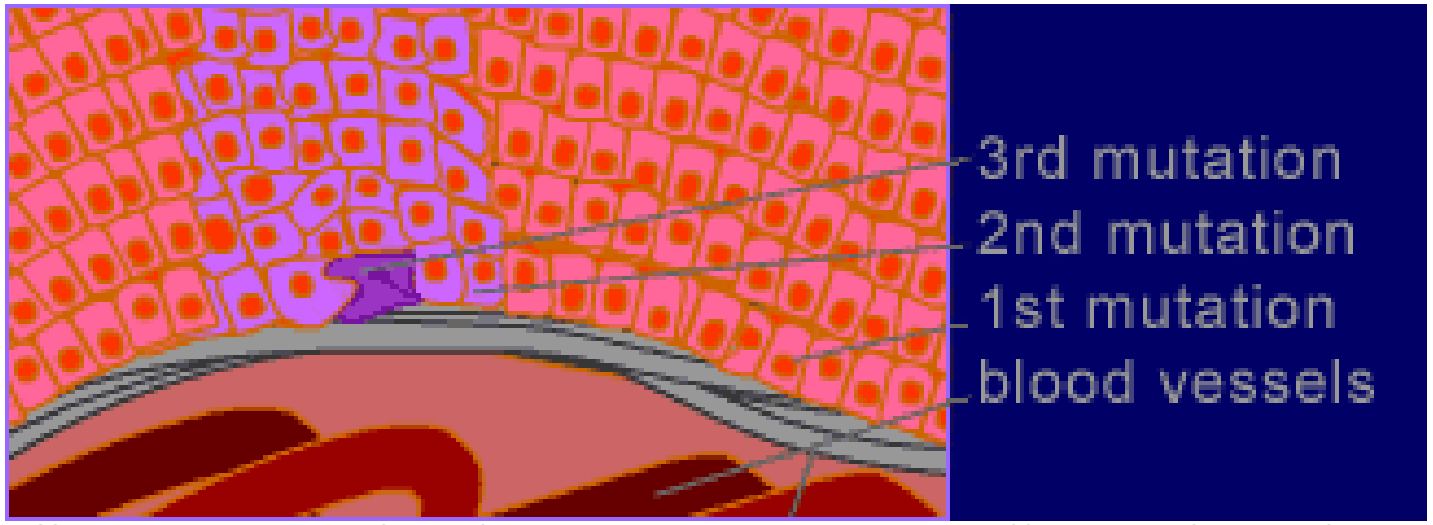
Spread and second mutation



- The genetically altered cells have, over time, reproduced unchecked, crowding out the surrounding normal cells. The growth may contain one million cells and be the size of a pinhead. At this point the cells continue to look the same as the surrounding healthy cells.

  After about a million divisions, there's a good chance that one of the new cells will have mutated further. This cell, now carrying two mutant genes, could have an altered appearance and be even more prone to reproduce unchecked.

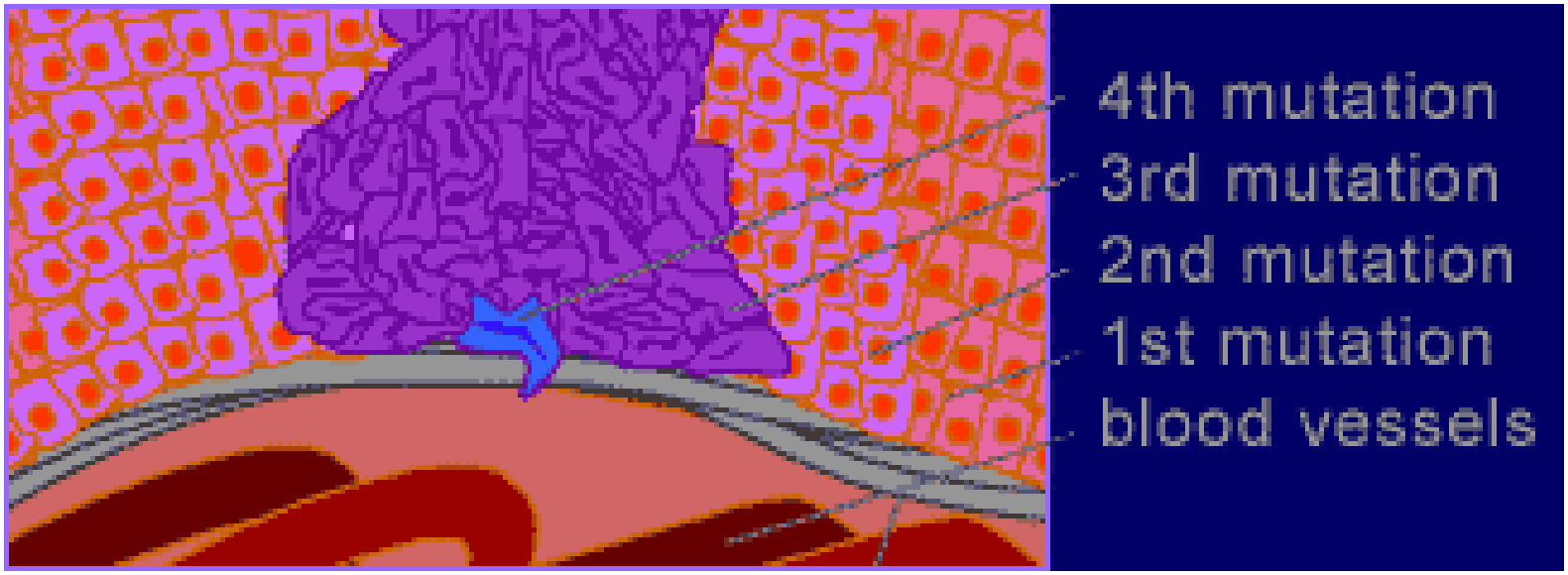
Third mutation



- Not all mutations that lead to cancerous cells result in the cells reproducing at a faster, more uncontrolled rate. For example, a mutation may simply cause a cell to keep from self-destructing. All normal cells have surveillance mechanisms that look for damage or for problems with their own control systems. If such problems are found, the cell destroys itself.

  Over time and after many cell divisions, a third mutation may arise. If the mutation gives the cell some further advantage, that cell will grow more vigorously than its predecessors and thus speed up the growth of the tumour.

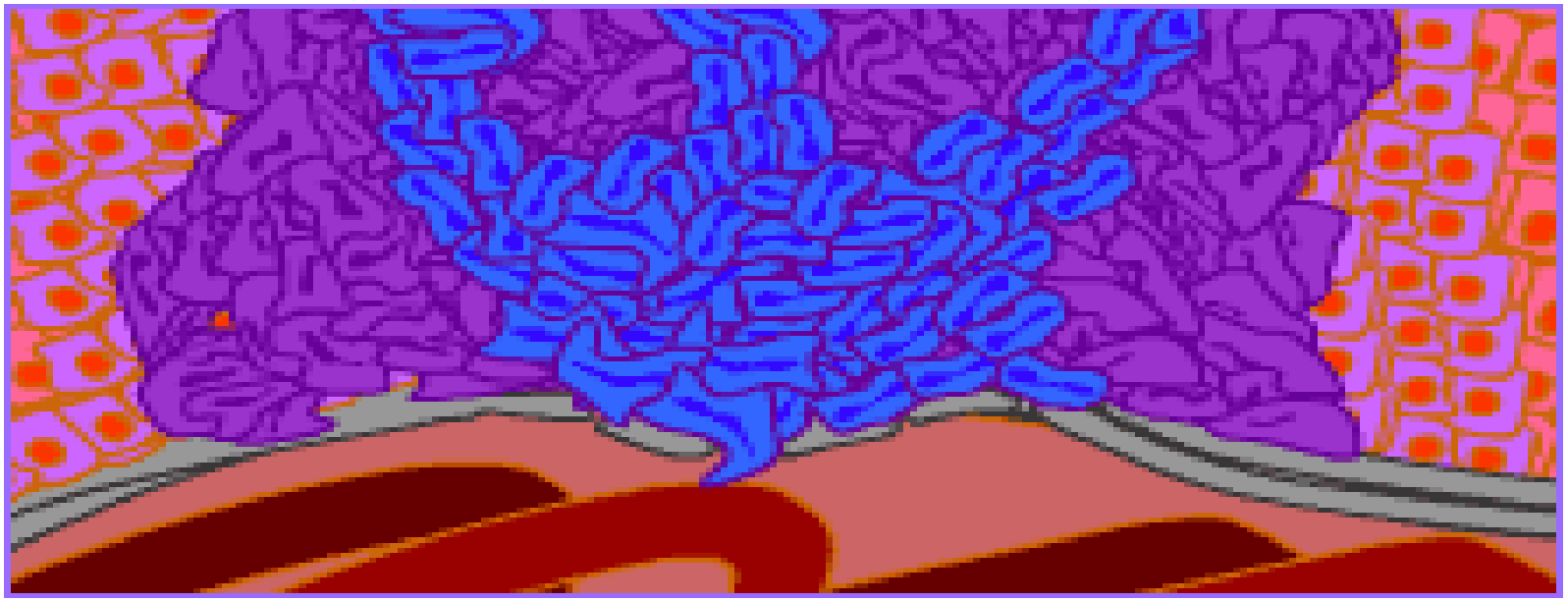
Fourth mutation



- The new type of cells grow rapidly, allowing for more opportunities for mutations. The next mutation paves the way for the development of an even more aggressive cancer.

  At this point the tumour is still contained.

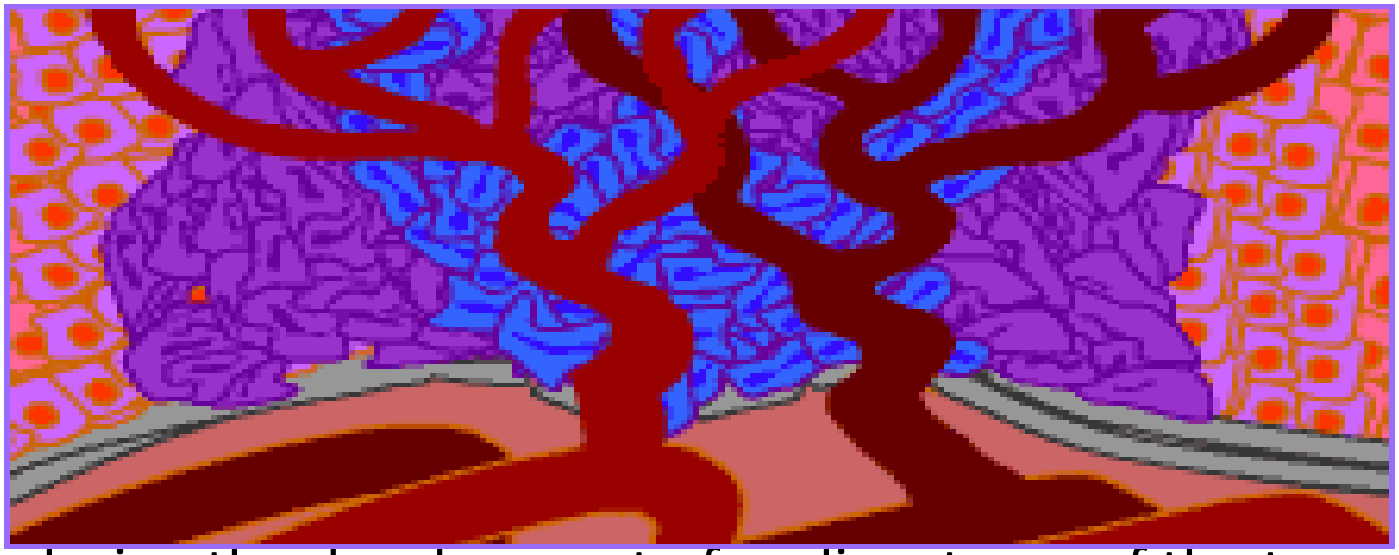
Breaking through the membrane



- The newer, wilder cells created by another mutation are able to push their way through the epithelial tissue's basement membrane, which is a meshwork of protein that normally creates a barrier. The invasive cells in this tumour are no longer contained.

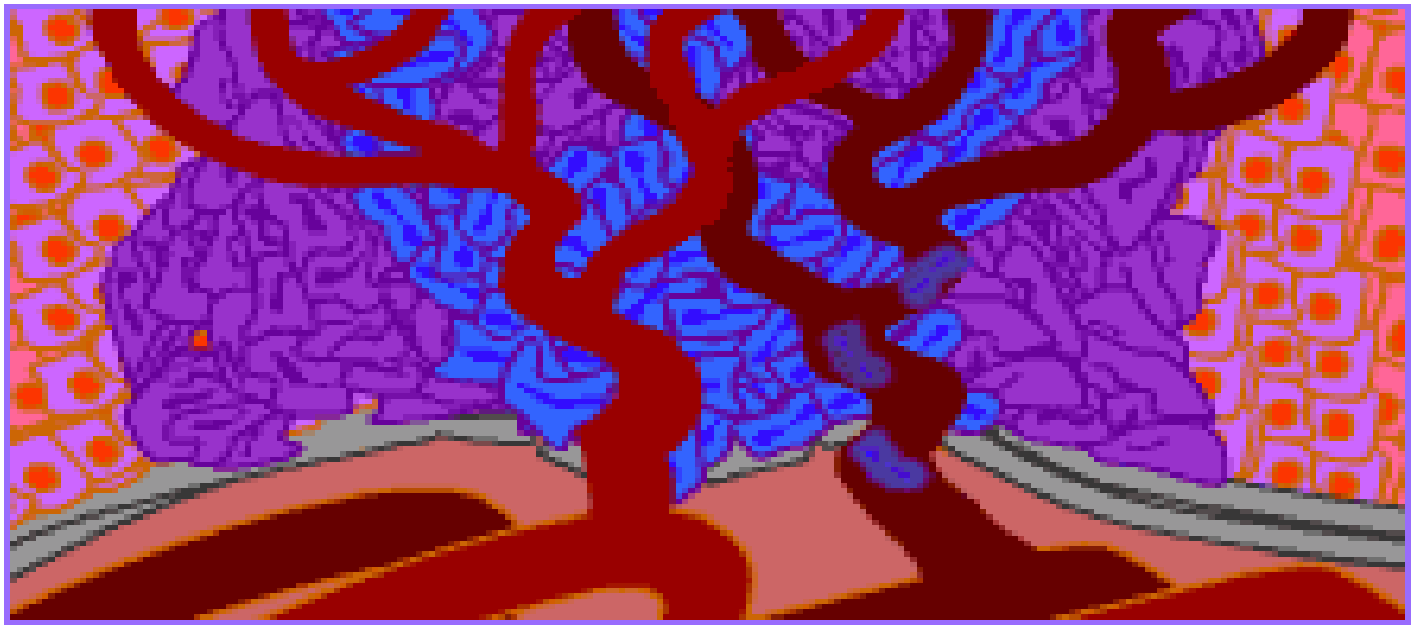
  At this point the cancer is still too small to be detected.

Angiogenesis



- Often during the development of earlier stages of the tumour, or perhaps by the time the tumour has broken through the basement membrane (as pictured above), angiogenesis takes place. Angiogenesis is the recruitment of blood vessels from the network of neighbouring vessels.
- Without blood and the nutrients it carries, a tumour would be unable to continue growing. With the new blood supply, however, the growth of the tumour accelerates; it soon contains thousand million cells and, now the size of a small grape, is large enough to be detected as a lump

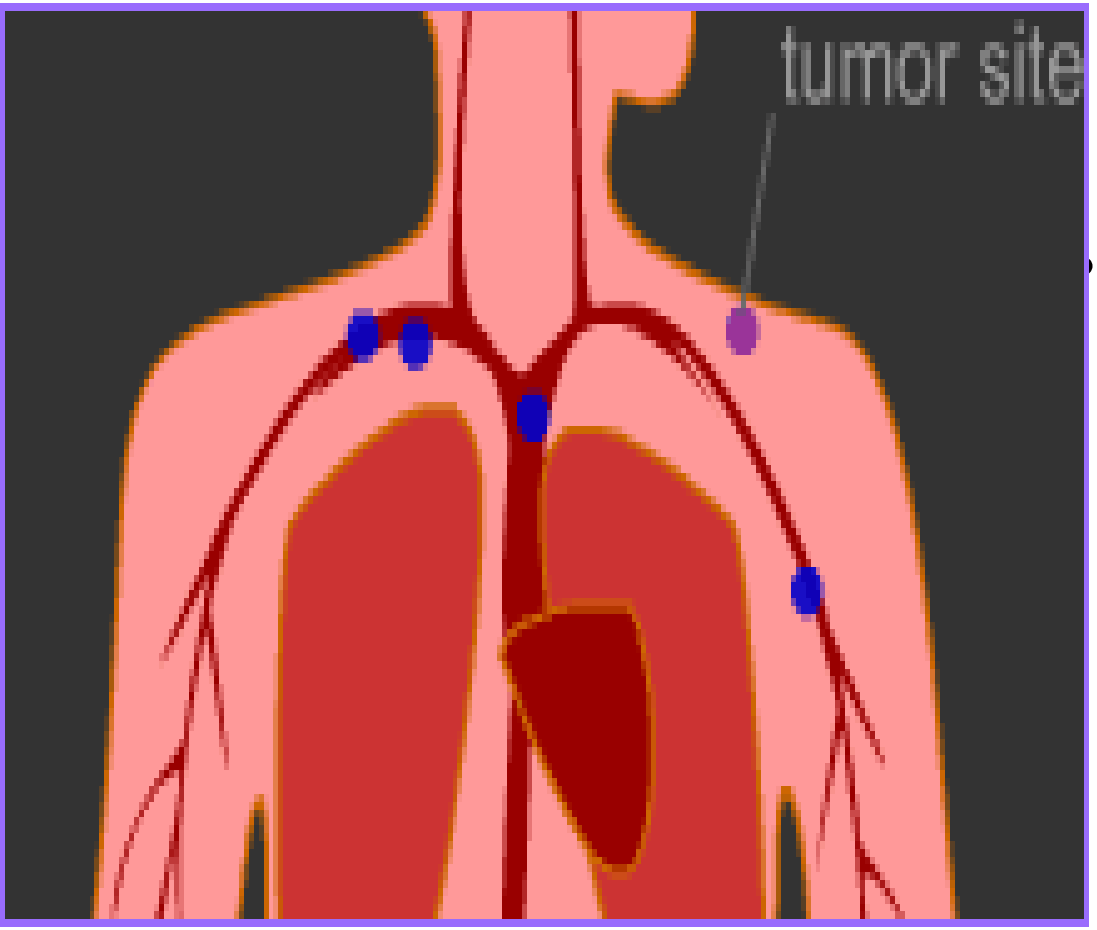
Invasion and dispersal



- The tumour has now invaded the tissue beyond the basement membrane.

  Individual cells from the tumour enter into the network of newly formed blood vessels, using these vessels as highways by which they can move to other parts of the body. A tumour as small as a gram can send out a million tumour cells into blood vessels a day.

Tumour cells travel - metastasis



- What makes most tumours so lethal is their ability to metastasize -- that is, establish new tumour sites at other locations throughout the body.
Secondary tumours.

- Metastasis is now underway, as tumour cells from the original cancer growth travel throughout the body. Most of these cells will die soon after entering the blood or lymph circulation.

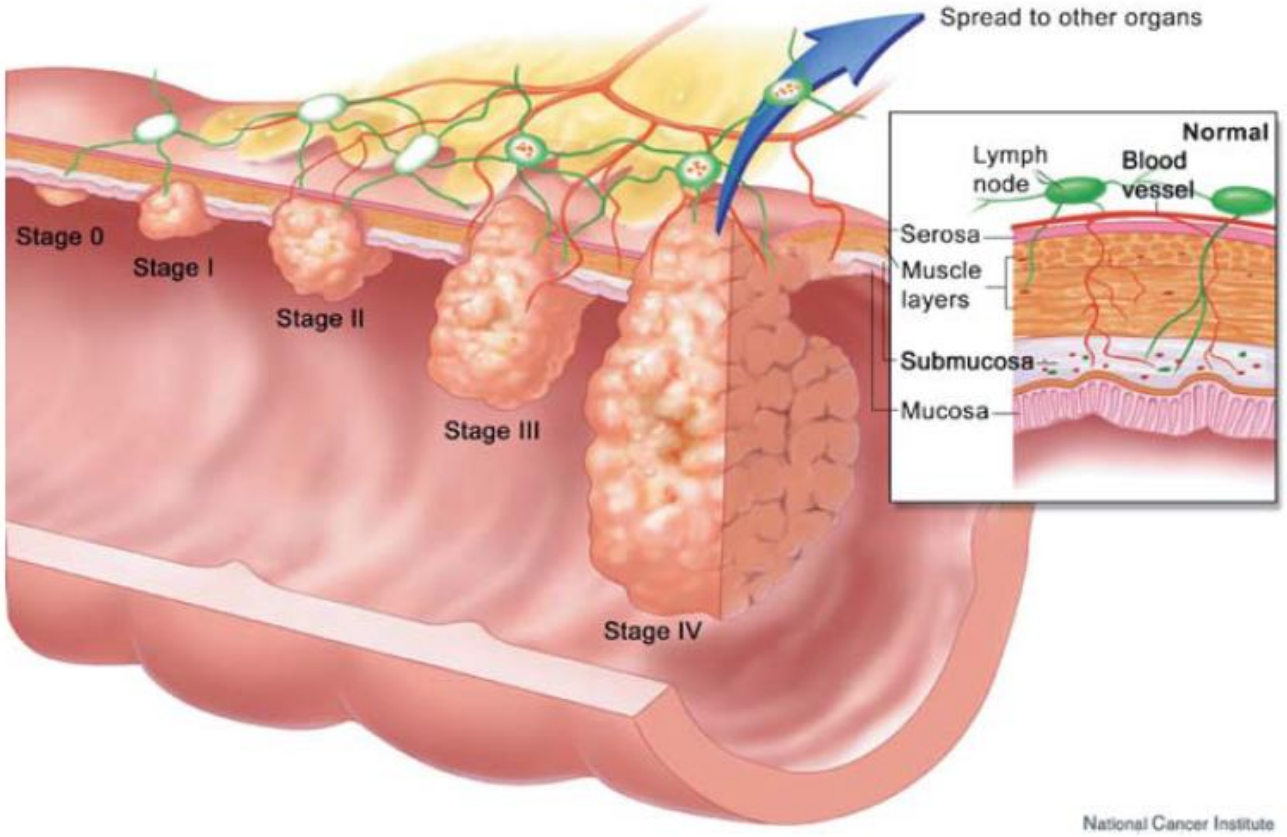


Fig. 1.21 Progressive growth of colorectal tumors. Early-stage tumors are confined to the mucosa. Growing tumors progressively invade the submucosa and muscular layers of the bowel, eventually penetrating the mesenteric vasculature (red) and lymphatic ducts (green). (Illustration by Terese Winslow, courtesy of the National Cancer Institute.)

Chronic inflammation and cancer predisposition

- Many cancers are preceded by a local inflammatory response to an infectious agent

Infectious agent	Type	Inflammatory disease	Cancer
Hepatitis B virus Hepatitis C virus	DNA virus	Hepatitis	Liver cancer
Helicobacter pylori	Bacterium	Gastritis	Stomach cancer
Epstein–Barr virus	DNA virus	Mononucleosis	B-cell, non-Hodgkin's lymphoma Burkitts lymphoma
Human Papillomavirus	DNA virus	Cervicitis	Cervical cancer
Schistosoma haematobium	Trematode	Cystitis	Bladder cancer
Opisthorchis viverrini	Flatworm	Cholangitis	Bile duct cancer

Mutations that occur in cancers fall into two functional categories:

- Drivers: mutations that are required for tumorigenesis
- Passengers: mutations that merely occur during tumorigenesis and do not contribute to the process.

Genetic alterations drive colorectal tumorigenesis